

Please amend claim 15 as follows:

C2  
C3  
15. (twice amended) The device of claim 13 further comprising a system for adding said chemical substance to the to the neural or muscle tissue sample in an [unknown] arbitrary concentration.

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Please amend claim 16 as follows:

C3  
16. (amended) The method of claim 12 for testing the effect on neural or muscle tissue samples of chemical substances as medicines, wherein the [step] chronic measuring step [after the step of adding a chemical substance to the neural or muscle tissue sample] takes place at least three days after said addition step.

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Applicants have amended claim 16 to clarify the wording of the claim. The remainder of the amendments are simply to specify the claimed invention, not to overcome any specific piece of prior art.

#### COMMENTS

The invention here is both a process and a device for observing or measuring the differences found in a tissue sample -- neural or muscle -- when the sample is contacted with a chemical substance which may be useful as a medicine. By measuring and comparing the differences, the overall efficacy or the specific efficacy of a chemical substance as a medicine may be determined. The microelectrodes are coated in such a way that the adhesion between the tissue sample and the microelectrodes is enhanced and thereby allows measurement of the effect at a time which is considered chronic.

### **New Matter Objection**

Claims 12 and 16 have been objected to by the Examiner for allegedly containing new matter. Specifically the Examiner points out that claim 12 recites:

“chronic effect”, “chronic response”, “electrodes coated with collagen covering” and in claim 16, “measuring sample at least 3 days after addition step.”

Applicants decline to cancel the material suggested to be new matter. Specifically, the concept of measuring chronic effects and chronic responses is found at a variety of sites throughout the specification, but, for example, at pages 29, at the end of the first full paragraph (comparing “acute” effect to “chronic” effect) and at page 30, line 7. Further, the measurement of a chronic effect after three days is shown at page 29.

### **35 U.S.C. § 112, Second Paragraph**

Claims 12 and 14-16 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. In support of the rejection, the Examiner suggests:

Claim 12 is rejected as being vague and indefinite for the recitation of “chronic,” and “chronic response.” What are the metes and bounds of “chronic” and “chronic response” Is it months or days? If this method is testing the effect of medicines on chronic neural or muscle tissue samples, how many times is this medicine being added to the culture? Is this medicine stable for a chronic culture? What are these chemical substances that are used as medicines?

Does electric stimulus have any effect on the neural or muscle tissue?

Claims 14 and 15 are rejected as being vague and indefinite for the recitation of “unknown concentration.” If unknown concentration of medicines are added to the culture, how the effect is compared with different medicines?

Claim 16 is confusing. The recitation of “wherein the step chronic measuring after the step of adding a chemical substance to the neural or

muscle tissue sample takes place at least three days after said addition step. Does applicant intend to say "The method of claim 12 for testing the chronic effect on neural or muscle tissue samples of chemical substances as medicine, wherein said chronic means at least three days after addition of medicine.

Applicants disagree. The term "chronic" and its contrasting term "acute" as used in the specification and in the claims are quite well known terms. Just because a term is broad does not mean that it is vague or indefinite. Attached are copies of definitions of the terms from Dorland's Medical Dictionary for the Examiner's information.

Withdrawal of the rejection is requested.

**35 U.S.C. § 103(a)**

Claims 2-16 stand rejected under 35 U.S.C. § 103 as unpatentable over Nisch et al. (Biosense.Bioelect 1994, 9:737-741). In support of the rejection, the Examiner notes:

Claims are directed to medicine testing device and a method of testing the chronic effect on neural or muscle tissue samples using the said device. The device comprises a plurality of microelectrodes coated with collagen and a visible property detection system.

Nisch et al describes a method which comprises a detector for detecting electrical properties of neuronal activity in vitro (page 738-739). He measures a detectable electrical signal before and after stimulation in figure 7 which is observed (*i.e.*, visible property). He further describes a testing device comprising electrical measurement portion (*i.e.*, visible) visible detection portion (Figure 3-monitor, figure 4, figure 5, figure 6, etc).

Nisch et al does not teach that the method and device are used for tissues. However, Stedman's Medical Dictionary defines tissue as "a collection of similar cells and the intercellular substances surrounding them. There are four basic tissues in the body: 1) epithelium; 2) the connective tissue, including blood, bone, and cartilage; 3) muscle tissue; and 4) nerve tissue. In addition, while the specification puts forth preferred embodiments, the specification does not define or restrict the term tissue to a particular

embodiment. Therefore, based on Stedman's Medical Dictionary the term tissue encompasses blood, which are single cells floating.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the Nisch et al method and device with a reasonable expectation of success because use of this method and device for tissue culture system are readily available. An artisan of ordinary skills would have been motivated to make such a device and method for measuring the electrical properties of tissues before and after the addition of medicine or drugs because it would have helped in determining the toxicity of the drug on tissue as taught by Nisch et al.

Applicants' arguments filed on 6/27/2000, have been fully considered but they are not deemed to be persuasive. Applicant argues that Nisch et al does not suggest the use of or suitability for placement of a tissue slice and medicine on collagen coated microelectrodes in an array. Examiner disagrees with the applicant. The art teaches that the attractive technique of this device is to record extracellular electrophysiological potentials with thin film microelectrode array in to the floor of tissue chamber (see page 737, first paragraph) and further this technique can be carried out in sterile chambers (see page 737 first and second paragraphs) using large number of neurons. Furthermore, the prior art teaches (page 737, second paragraph) the device had to be biocompatible, resistant to a saline environment and sterilization and easily maintained in cell culture conditions. Therefore, one could place tissue and medicine in those chambers. To increase adhesion, electrodes are coated with Cr and then gold (*i.e.*, collagen coated microelectrodes: new matter). Further Nisch suggests that (page 737, first paragraph) monitoring extracellular neuronal activity in vitro over extended periods of time should be helpful in answering many questions about neuronal network development and function. It would be obvious for a person of ordinary skill in the art at the time invention was made to use Nisch's device and method for measuring electrical properties of tissues before and after addition of medicine or drugs for a long time because Nisch teaches this device and method are useful for measuring electrical or visible properties of neurons and hence one could use this for neural or muscle tissue. The claimed invention is *prima facie* obvious in view of the prior art absent any convincing evidence to the contrary. Therefore, this rejection is maintained.

Each of the claims require some unique feature which inures to the benefit of comparing one state of a neural or muscle tissue sample to another state. For instance,

each of the claimed devices necessarily requires that the microelectrode service be coated with a material which increases the adhesion of that slice to the microelectrode surface. A similar limitation is found in each of the method claims.

The Examiner admits that Nisch et al does not teach that the methods described in the article are used for “tissues.” The Examiner’s discussion of blood as a tissue is consequently not apparently germane to the claims at issue, either before or after the current amendment. Since Nisch et al does not suggest the use of the device or method described in the article on a tissue slice, it is indeed difficult to make the jump in logic proposed in the Office Action. Specifically, it is unclear why one of ordinary skill in this art would find it appropriate to measure the electrophysiological potentials of the tissues as opposed to those of the individual cells proposed by Nisch et al. Further, since Nisch fails to teach the use of a material intended to improve the adhesion of a slice to the microelectrodes, but instead maintains a soup of individual cells, the Examiner’s argument is without basis.

Further discussing the Examiner’s note that blood is a tissue: if this is considered an appropriate use of the term “tissue”, how then does one of ordinary skill in this art tell the difference in the literature between a truly large, harvested tissue slice and a single cell. Perhaps the Examiner could suggest some reasonable use of the noted terminology which is acceptable. It is believed that the terms found in the claims -- “neural or muscle tissue samples” and measurement of “electrical properties” of those “samples -- should be sufficient, but if there are better terms, please let us know.

The Examiner’s suggestion that one “could place” tissue and medicine in the chambers of Nisch et al is without appropriate basis in law. The supervising court, and indeed the MPEP, specifically prohibit such “obvious to try” and “given the invention, it

would be apparent to do something with the invention” type arguments as support for rejections under 35 USC 103.

The suggestion that “to increase adhesion, electrodes are coated with chromium and then gold...” bypasses the functional limitation of the current claims -- an adhesive material is added to the microelectrode surface to enhance the adhesion of the sample to the microelectrode surface. The specific teaching of Nisch et al do not talk of increasing the adhesion of the cells studied there. Nisch speaks only of adding (at page 738, second column) ten nanometers of chromium to increase the adhesion of the gold used in the microelectrode array. Nothing is said of any procedure or material being used to increase the adhesion of any tissue of any kind.

Finally, since there is no suggestion that the device as described in Nisch et al was ever used on a cell or on a tissue sample -- note, for instance, in figure 7, that signals are “simulated” and that no specific mention of anything other than the electrical characteristics of the device itself -- it is most unlikely that it is predictable that the Nisch et al device can be used to measure chronic effects on tissue samples.

Applicants request withdrawal of the rejection.

### **Judicial Double Patenting**

Claims 12-16 stand rejected under the judicially created doctrine of obviousness - type double patenting as patentable over Claims 1-13 of U.S. Patent No. 5,563,067. As a part of the rejection the Examiner suggests:

Although the conflicting claims are not identical, they are not patently distinct from one another because both claims of the instant application and those of U.S. Patent No. 5,563,067 are drawn to apparatus and a method of measuring the electrical and physical characteristics of cells. While 1 to 13 of U.S. Patent No. 5,563,067, specifically recited apparatus for measurement of electric and physical characteristics of cells (sic). It does not specifically recite measuring the properties of tissue with or

without addition of medicines. However, it would have been obvious to one of ordinary skill in the art to substitute any tissue in the claim methods of device in order to measure electrical and physical properties of tissue with or without addition of medicines.

Applicants disagree. The Office Action has provided no basis in technology why one would make the described jump of logic. For instance, each of the claims require the presence of material enhancing the adhesion of the tissue to the microelectrode plate. If it would have been obvious to add the adhesive material, it is incumbent on the Office Action to recite a reference to bridge the gap between the claims of the prior patent and the claims recited herein. Withdrawal of rejection is therefore requested.

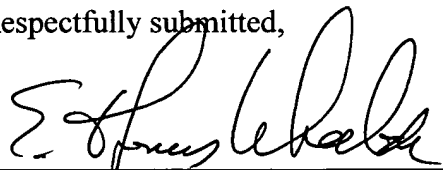
### CONCLUSION

Applicants have responded to each issue of substance raised in the Office Action. Allowance of the application is now requested. Should the Examiner have any additional comments, questions, or requests, the Examiner is requested to contact applicants' attorney at the number listed below. Should a personal or telephonic interview be desired, again, please contact applicants' attorney and accommodation will be made.

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Respectfully submitted,

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